way as to enable one skilled in the art to which it pertains to make and use the invention. The Examiner supports the rejection by stating that:

1.) the present claims encompass "any molecule" that may induce an immune response;
2.) no tumor antigens are disclosed in the specification which may be effective in the treatment of cancer;
3.) the present claims read on methods of treating one type of cancer with tumor antigens of another cancer type; and,
4.) the identification of "antigenic molecules" for use as effective agents as an immunotherapeutic composition in the treatment of cancers would not have been routine to one of ordinary skill in the art at the time the invention was made.

In addition, the Examiner cites *Falo, et al.* as representative of the state of the art at the time the application was filed and to illustrate the degree of predictability in the art. The Examiner states *Falo* teaches that there are two major hurdles that must be overcome for effective cancer vaccine development: first, tumor antigens recognized by CTLs must be identified, and second, CTL responses to the tumor antigens must be evident. Based upon the above statements, the Examiner concludes that the specification does not provide sufficient guidance for one skilled in the art to use the invention without undue experimentation. In light of the above amendments and following remarks, Applicants respectfully disagree.

As a preliminary matter, Applicants wish to emphasize that the presently claimed invention is not a cancer vaccine *per se*, and the role of flt3-ligand is more akin to an adjuvant, immunomodulator, immunopotentiator, and the like. As such, the Examiner's description of the claimed invention as an "anti-tumor vaccine" is a mischaracterization of Applicants' invention, and consequently the Examiner's reliance on *Falo, et al.* is improper. Nevertheless, in order to facilitate prosecution, Applicants will address each of the Examiner's points.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent *coupled with what is known in the art* without undue experimentation. Applicants note that a patent need not teach, *and preferably omits*, what is well known in the art *(In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d1331, 1332 (Fed. Cir. 1991)). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue (*In re Angstadt*, 537 F.2d 498,504, 190 USPQ 214, 219 (CCPA 1976)). As to what constitutes undue experimentation, a factual determination of the factors described by the *Wands* Court (see, MPEP 2164.01(a)) is to be

performed. In short, Applicants submit that one of skill in the art would not have to undertake undue experimentation to practice the claimed methods because tumor antigens and methods of administering tumor antigens to treat cancer in patients were known in the art, and the further requirement of administering flt3-ligand in conjunction with a tumor antigen would not constitute undue experimentation.

The specific issues raised by the Examiner concerning Applicants' disclosure in light of the *Wands* factors will be addressed in detail in the following discussion.

Examiner's Point #1:

As described above, Applicants have amended the claims in an effort to expedite prosecution and present the claims in condition for allowance. In particular, the claims have been amended to specify that the antigen being administered is a *tumor* antigen, and therefore, do not read on "any molecule" that may induce an immune response. As such, Applicants respectfully submit that the amended claims render the Examiner's first point moot.

Examiner's Point #2:

Applicants respectfully traverse the Examiner's contention that the specification does not provide sufficient guidance to enable one of skill in the art to make and use the presently claimed invention because "no tumor antigens are disclosed in the specification which may be effective in the treatment of cancer." Applicants note that a large number of tumor antigens were well known in the art at the time the application was filed and that the present specification need not teach what was already known in the art. For example, one of skill in the art would be familiar with known tumor antigens such as overexpressed Her-2/neu (breast, ovarian and other carcinomas); MAGE, MART, BAGE, GAGE and gp100 (proteins expressed in melanomas and many carcinomas); PSA (Prostate Specific Antigen – prostate carcinomas); and *CEA* (Carcinoembryonic antigen expressed on many tumors). In support of this fact, Applicants direct the Examiner's attention to Table 1 at page 123 of the previously provided reference "Cancer Vaccines: Novel Approaches and New Promise", Minev, B., et al., *Pharmacol. Ther.*, Vol. 81, No. 2, pp. 121-139, 1999, which provides a *partial* list of human tumor antigens *recognized by T lymphocytes*, their MHC restriction, peptide epitope and tumor type, as well as *dated references for each tumor antigen.* Throughout the article, the authors discuss various studies showing tumor-specific CTL immune responses for many of the tumor antigens. Furthermore, the *Falo* reference cited by the Examiner states at page

1041, second column that "... significant progress has been made in defining the peptides recognized by tumor-specific CTLs." and that "[p]eptide antigens have been defined for several human tumors and MHC class I alleles", and proceeds to list numerous examples.

Clearly, defined tumor antigens with known CTL epitopes were well known in the art at the time the application was filed. It is certain that one of skill in the art of cancer vaccines, adjuvants and other related fields would be familiar with published tumor antigens and would readily apply this knowledge in making and using the presently claimed invention. Applicants note that the law does not "require" a patent to reiterate what is known in the art. Therefore, Applicants respectfully submit that the present specification is fully enabling to the skilled artisan. As such, Applicants respectfully request the rejection under 35 U.S.C. §112, first paragraph be properly withdrawn.

Examiner's Point #3.

The Examiner's third point states that the present claims read on methods of treating one type of cancer with tumor antigens of another cancer type. Applicants respectfully submit that the present claims need not describe factors that one of skill in the art would consider obvious. This issue has been made clear by the courts; the court in *In re Skrivan* stated:

> Claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art: **the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious**. *In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970).

Applicants submit that it is a fundamental tenet of immunology and vaccinology that an immunoprotective response is typically generated against a disease by immunizing the subject with an antigen that is immunologically relevant to the disease being treated. This was established by Edward Jenner in 1798 and has been applied consistently in the development of vaccines for such diseases such as measles, polio, hepatitis, etc, as well as cancer vaccines. Applicants submit as evidence Exhibits B, C and D, which are clinical trial protocols in which tumor antigens relevant to the cancer being treated are administered to the patients. Specifically, Exhibit B describes administering flt3-ligand and melanoma tumor antigens for the treatment of melanoma; Exhibit C describes administering flt3-ligand as an adjuvant in combination with a HER-2/neu antigens for the treatment of prostate cancer; and, Exhibit D is cancer vaccine protocol using flt3-ligand as an adjuvant in combination with

HER-2/neu tumor antigens for the treatment of breast or ovarian cancer. These clinical trial references demonstrate that clinicians typically administer cancer antigens that are relevant to the patients' disease. As such, Applicants submit that the claims need not recite factors that skilled clinicians would consider obvious, namely treating patients with an antigen that is immunologically relevant to the disease being treated. Furthermore, the presence of inoperable embodiments within the scope of a claim does not necessarily render a claim nonenabled. As a final note, Applicants draw the Examiner's attention to page 10, lines 1-14, and especially line 5, which states that "the antigen may be one that already exists within the patient, such as a tumor antigen....." This disclosure clearly supports embodiments of the claimed method wherein the tumor antigen(s) administered to the patient are related to the patient's cancerous or neoplastic disease.

Examiner's Point #4.

The final point raised by the Examiner states that the identification of "antigenic molecules" for use as effective agents as an immunotherapeutic composition in the treatment of cancers would not have been routine to one of ordinary skill in the art at the time the invention was made. Applicants have addressed this issue in the discussion above, noting that a large number of tumor antigens were well known in the art at the time the application was filed and that the present specification need not teach what was already known. As such, one of skill in the art would not have to identify antigenic molecules for use in the presently claimed invention because tumor antigens were already identified. The Examiner is invited to review the "Cancer Vaccines: Novel Approaches and New Promise" reference which supports Applicants' statements. Furthermore, Applicants note that "[I]f a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied (*In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960)). Applicants respectfully submit that numerous tumor antigens were well known in the art, as well as recognized modes of administration, and therefore stress that one of skill in the art would be able to make and use the present invention with minimal application of routine, established methodologies. Indeed, given that the level of ordinary skill in the relevant art is quite high, it cannot be considered undue experimentation to administer a known tumor antigen using standard methodologies in conjunction *with Flt-3-ligand* (as variously claimed). Thus, Applicants submit the present specification satisfies the enablement requirement and the rejection under 35 U.S.C. §112, first paragraph may be properly withdrawn.

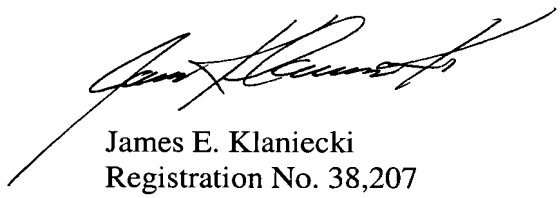
The Examiner states that, due to the unpredictability in the relevant art, the subject specification does not provide sufficient guidance for one skilled in the art to use the claimed invention without undue experimentation. In support of this position the Examiner cites *Falo*, which teaches, *inter alia*, that there are two major hurdles that must be overcome for effective cancer vaccine development: first, tumor antigens recognized by CTLs must be identified, and second, CTL responses to the tumor antigens must be evident. As discussed above, *Pharmacol. Ther.* teaches that many tumor antigens recognized by CTLs had been identified at the time the subject application was filed, and that several animal models had shown the efficacy of cancer vaccines. This demonstrates the state of the art at the time the invention was made was quite advanced, and consequently, the art had a higher level of predictability than suggested by the Examiner.

Applicants' position is supported by *in vivo* experiments and clinical trials that use the claimed methods. Specifically, Exhibit A is an abstract summarizing the results of a *in vivo* study performed at the University of Washington in 1998 using flt3-ligand as a vaccine adjuvant in combination with immunization with a tumor antigen (HER2 protein). The study showed that flt3-ligand, when used as the sole adjuvant in a tumor antigen-based vaccine, is a potent stimulator of an IFNγ-producing, antigen specific T-cell response. Significantly, numerous human clinical trials using the claimed methods are currently underway. For example, Exhibit B is an excerpt from a LICR protocol for a Phase I/II clinical trial for administering flt3-ligand and melanoma tumor antigens; Exhibit C describes a Phase I clinical trial of flt3-ligand as an adjuvant in combination with a HER-2/neu peptide-based cancer vaccine for advanced stage prostate cancer; and, Exhibit D describes a Phase I clinical trial using flt3-ligand as an adjuvant in combination with HER-2/neu peptide-based cancer vaccine and GM-CSF for breast or ovarian cancer.

Applicants submit that the fact that numerous clinical trials are using the claimed methods is compelling evidence that the art is not so unpredictable as to preclude one of ordinary skill in the art from practicing the claimed invention. In addition, such studies demonstrate that one of skill in the art would not have to perform undue experimentation to practice the claimed invention. In short, the animal studies and clinical trials demonstrate that there is a reasonable expectation of success in using the claimed invention. Applicants note that human clinical trial data enjoys a heightened status because the Applicants have provided a convincing rationale to those *especially* skilled in the art, i.e., the FDA, that the investigation may be successful (see MPEP 2107.02 IV). As such, the rejection under 35 U.S.C. §112, first paragraph is without merit and should be properly withdrawn.

Reconsideration and allowance of pending claims 6, 7, 20 and 22-56 is kindly requested.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: Kenneth A. Brasel, Stewart D. Lyman, Eugene Maraskovsky, Hilary J. McKenna, David H. Lynch and Charles R. Maliszewski

Docket No.: 2836-D

Group Art Unit: 1644

Examiner: F.P. VanderVegt

Serial No: 09/448,378

Filed: November 23, 1999

CPA Filed: June 28, 2001

For: DENDRITIC CELL STIMULATORY FACTOR

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

6. (Twice amended) A method for augmenting an immune response in a patient having a cancerous or neoplastic disease, comprising the steps of administering flt3-ligand in an amount sufficient to generate an increase in the number of the patient's dendritic cells and administering ~~an~~ a tumor antigen to the patient.

20. (Twice amended) A method of treating cancerous or neoplastic disease in a patient in need thereof comprising administering ~~Flt3-L~~ flt3-ligand in an amount sufficient to enhance the patient's immune response to such disease and administering ~~an~~ a tumor antigen to the patient.

22. (Amended) The method of claim 6, wherein the ~~flt-3~~ flt3-ligand is ~~soluble~~ human ~~flt-3~~ flt3-ligand.

23. (Amended) The method of claim 22, wherein the ~~flt-3~~ flt3-ligand is soluble human ~~flt-3~~ flt3-ligand.

24. (Amended) The method of claim 23, wherein the soluble human ~~flt-3~~ flt3-ligand is recombinant ~~flt-3~~ flt3-ligand.

25. (Amended) The method of claim 24, wherein the soluble human ~~flt-3~~ flt3-ligand has an amino acid sequence that is encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to, and is at least 80% identical to, a nucleic acid that encodes an amino acid sequence selected from the group consisting of amino acids 28 to Xaa of SEQ ID NO:2 and amino acids 28 to Yaa of SEQ ID NO:1, wherein Xaa is an amino acid from 163 to 231, and Yaa is an amino acid from 160 to 235.

26. (Amended) The method of claim 24, wherein the soluble human ~~flt-3~~ flt3-ligand comprises an amino acid sequence selected from the group consisting of amino acids 28 to Xaa of SEQ ID NO:2 and amino acids 28 to Yaa of SEQ ID NO:1, wherein Xaa is an amino acid from 163 to 231, and Yaa is an amino acid from 160 to 235.

27. (Twice amended) The method of claim 6, wherein the ~~flt-3~~ flt3-ligand has the amino acid sequence of residues 28-163 of SEQ ID NO:2.

28. (Twice amended) The method of claim 26, wherein the soluble human ~~flt-3~~ flt3-ligand has the amino acid sequence of residues 28-160 of SEQ ID NO:1.

29. (Twice amended) The method of claim 6, wherein the ~~flt-3~~ flt3-ligand has the amino acid sequence of residues 28-188 of SEQ ID NO:2.

30. (Twice amended) The method of claim 26, wherein the soluble human ~~flt-3~~ flt3-ligand has the amino acid sequence of residues 28-182 of SEQ ID NO:1.

31. (Amended) The method of claim 20, wherein the ~~flt-3~~ flt3-ligand is ~~soluble~~ human ~~flt-3~~ flt3-ligand.

32. (Amended) The method of claim 31, wherein the ~~flt-3~~ flt3-ligand is soluble human ~~flt-3~~ flt3-ligand.

33. (Amended) The method of claim 32, wherein the soluble human ~~flt-3~~ flt3-ligand is recombinant ~~flt-3~~ flt3-ligand.

34. (Amended) The method of claim 33, wherein the soluble human ~~flt-3~~ flt3-ligand has an amino acid sequence that is encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to, and is at least 80% identical to, a nucleic acid that encodes an amino acid sequence selected from the group consisting of amino acids 28 to Xaa of SEQ ID NO:2 and amino acids 28 to Yaa of SEQ ID NO:1, wherein Xaa is an amino acid from 163 to 231, and Yaa is an amino acid from 160 to 235.

35. (Amended) The method of claim 33, wherein the soluble human ~~flt-3~~ flt3-ligand comprises an amino acid sequence selected from the group consisting of amino acids 28 to Xaa of SEQ ID NO:2 and amino acids 28 to Yaa of SEQ ID NO:1, wherein Xaa is an amino acid from 163 to 231, and Yaa is an amino acid from 160 to 235.

36. (Twice amended) The method of claim 20, wherein the ~~flt-3~~ flt3-ligand has the amino acid sequence of residues 28-163 of SEQ ID NO:2.

37. (Amended) The method of claim 35, wherein the soluble human ~~flt-3~~ flt3-ligand has the amino acid sequence of residues 28-160 of SEQ ID NO:1.

38. (Twice amended) The method of claim 20, wherein the ~~flt-3~~ flt3-ligand has the amino acid sequence of residues 28-188 of SEQ ID NO:2.

39. (Amended) The method of claim 35, wherein the soluble human ~~flt-3~~ flt3-ligand has the amino acid sequence of residues 28-182 of SEQ ID NO:1.

44. (Amended) The method of claim 6, wherein the tumor antigen is in the form of a tumor cell bearing said tumor antigen ~~is a tumor cell~~.

45. (Amended) The method of claim 6, wherein the tumor antigen is in the form of an isolated tumor antigen ~~is a tumor antigen~~.

46. (Amended) The method of claim 6, wherein the antigen is administered prior to administering flt3-ligand ~~Flt3-L~~.

47. (Amended) The method of claim 6, wherein the antigen is administered concurrently with flt3-ligand ~~Flt3-L~~.

48. (Amended) The method of claim 6, wherein the antigen is administered after administering flt3-ligand ~~Flt3-L~~.

49. (Amended) The method of claim 20, wherein the tumor antigen is in the form of a tumor cell bearing said tumor antigen ~~is a tumor cell~~.

50. (Amended) The method of claim 20, wherein the tumor antigen is in the form of an isolated tumor antigen ~~is a tumor antigen~~.

51. (Amended) The method of claim 20, wherein the tumor antigen is administered prior to administering flt3-ligand ~~Flt3-L~~.

52. (Amended) The method of claim 20, wherein the tumor antigen is administered concurrently with administering flt3-ligand ~~Flt3-L~~.

53. (Amended) The method of claim 20, wherein the tumor antigen is administered after administering flt3-ligand ~~Flt3-L~~.

54. (Amended) A method of treating cancerous or neoplastic disease in a patient in need thereof comprising administering flt3-ligand ~~Flt3-L~~ to the patient, isolating dendritic cells from the patient, exposing the dendritic cells to ~~an~~ a tumor antigen, and administering the dendritic cells to the patient.

55. (Amended) The method of claim 54, wherein the tumor antigen is in the form of a tumor cell bearing said antigen ~~is a tumor cell~~.

56. (Amended) The method of claim 54, wherein the tumor antigen is in the form of an isolated tumor antigen ~~is a tumor antigen~~.